Peer review file

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Reviewer A

Comment -1

There are a number of English/language issues along with grammar and punctuation errors that need to be addressed throughout the manuscript.

Reply 1: To improve the quality of the manuscript, grammar and punctuation reviews were performed.

Comment-2

The meta-analysis appears to have been completed in the appropriate manner for the overall Comments of concurrent vs. sequential chemotherapy with hypofractionated RT. However, sequential CRT studies included were only those in which patients were treated with chemo first, followed by RT.

a. Were there any studies that treated patients in the reverse order that were not included but may have provided additional valuable data?

Reply 2a: In our meta-analysis, we focused our searches on finding papers only comparing HYPO-RT combined with chemotherapy in the sequential or concurrent form. Moreover, these two treatment sequences are more habitual in clinical practice, while the inverted sequence is not usual. We chose this strategy to collect data from similar trials, combining patient data to evaluate outcomes correlated with the prevailing clinical practice.

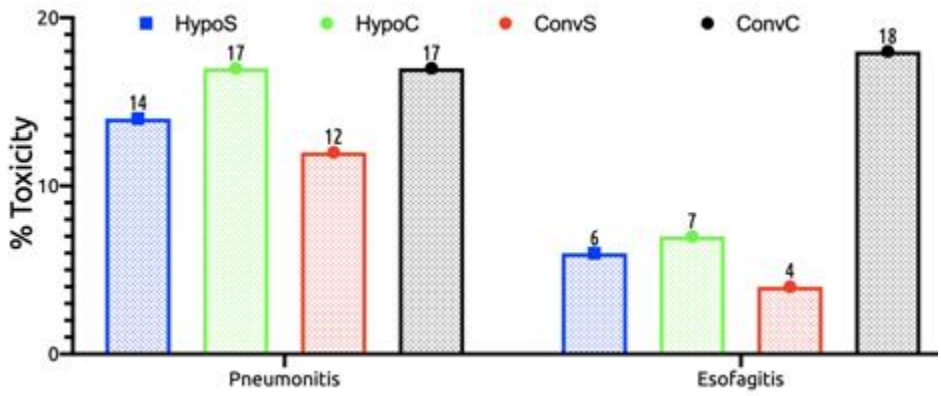
b. For the second part of this manuscript, which is the comparison between hypofractionated RT and conventionally-fractionated RT, it appears that the only conventional RT studies included were those in the Auperin meta-analysis. For a true comparison of data between these two groups, it would be far more regimented and complete to perform a second PRISMA search for the conventional RT studies, and/or to include any trials that are not included in the Auperin M-A and are more current.

Reply 2b: Our intention in comparing our meta-analysis of HYPO-RT with the data from Auperin CONV-RT meta-analysis was only to demonstrate the equivalence between the radiotherapy schedules. We choose the Auperin meta-analysis because it is considered the standard of treatment for more than ten years. Therefore, we used it as a reference to show our results and at the same time contextualize them. Our intention at any time was to perform two systematic reviews in the same work. Our PICO Comment is restricted to HYPO-RT combined with chemotherapy. We tried to make it more evident with the following sentence: "We utilized the data available from the meta-analysis performed by Auperin et al. Then, a subgroup analysis was performed dividing the studies by HYPO-RT versus CONV-RT."."

Comment 3:

The authors note that the efficacy and safety of hypofractionated RT with chemotherapy is being evaluated, but the endpoint of toxicity is not evaluated for the primary Comment of concurrent vs sequential CRT, so safety is not truly being evaluated. Moreover, for the comparison of toxicities between conventional and hypofractionated CRT, there is a brief mention of this in the Adherence and toxicity subsection of the Results, but this evaluation does not appear to be comprehensive, in part due to comments above regarding inclusion criteria for evaluation of conventionally-fractionated RT studies.

Reply 3: Thanks for the commentary. We introduced a figure showing the rates of grade 3 or higher esophagitis and pneumonitis. We believe that your suggestion helped us to clarify this point and that now it is clear that the HYPO-RT has a similar toxicity profile to CONV-RT. Many thanks.



Comment 4:
All tables and figures should include legends defining any abbreviations used. References for the two studies being compared in Table 1 should be included.

Reply 4: All tables and figures were revised and the abbreviations were put according to your recommendation.

Reviewer B

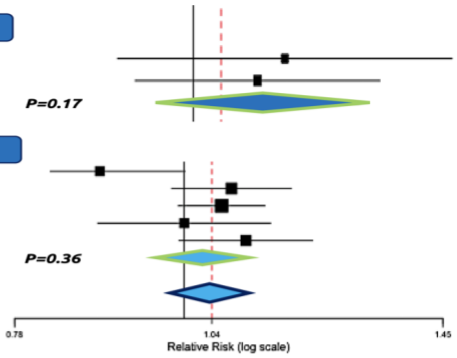
Comment: Given limited ability to compare all endpoints indirectly to conventional RT, I wonder if the authors were able to compare local failure rates between hypofractionated and conventional RT methods? If not, this may be mentioned in the discussion as it proposed as one of the benefits of hypofractionation.

Reply: Thank you very much for your suggestion. We introduced a figure providing data about the subgroup analysis only to compare to CONV-RT indirectly. It is possible to observe that there was a non-significant difference between the end-points.

(a) Overall mortality at 3 years

Studies	Estimate (95% C.I.)	HYPO-RT-S	HYPO-RT-C
SOCCAR 2014	1.14 (0.89, 1.45)	43/60	44/70
EORTC 2007	1.07 (0.92, 1.30)	66/78	63/80
Overall (I2=0%,P=0.1794)	*1.09 (0.96, 1.28)*	*109/138*	*107/150*

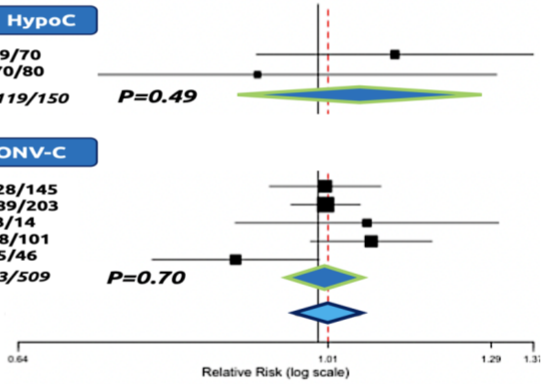
Studies	Estimate (95% C.I.)	CONV-S	CONV-C
CALGB8831	0.88 (0.78,1.00)	39/45	45/46
WJLCG	1.07 (0.98,1.16)	142/158	111/156
RTOG9410.	1.05 (0.99,1.12)	189/203	180/204
GMMA	1.00 (0.88,1.10)	15/15	15/15
GLOT	1.09 (0.99,1.20)	96/103	87/102
Overall (I2=52%,P=0.07)	*1.03 (0.96, 1.10)*	*481/524*	*458/523*



(b) Disease progression at 3 years

Studies	Estimate (95% C.I.)	HypoS	HypoC
SOCCAR 2014	1.11 (0.91, 1.37)	47/60	49/70
EORTC 2007	0.95 (0.83, ,1.08)	65/78	70/80
Overall (I2=0%,P=0.173)	*1.06 (0.89, 1.268)*	*112/138*	*119/150*

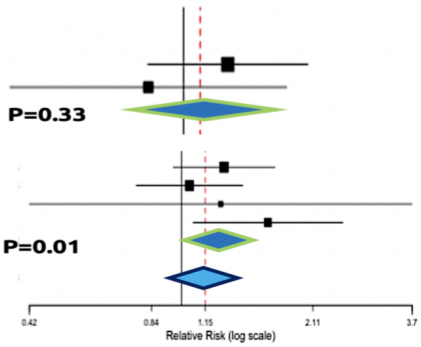
Studies	Estimate (95% C.I.)	CONV-S	CONV-C
WJLCG	1.01 (0.90,1.56)	132/148	128/145
RTOG 9410	1.01 (0.64,1.29)	192/204	189/203
GMMA	1.07 (0.52,1.89)	12/14	13/14
GLOT	1.08 (0.64,1.38)	97/103	88/101
CALGB	0.88 (0.78,1.00)	39/45	45/46
Overall (I2=42%,P=0.136)	*1.06 (0.89, 1.268)*	*474/514*	*463/509*



(c) Local failure at 3 years

Studies	Estimate (95% C.I.)	HypoS	HypoC
SOCCAR 2014	1.11 (0.91, 1.37)	47/60	49/70
EORTC 2007	0.91 (0.64,1.29)	33/78	37/80
Overall (I2=0%,P=0.330)	*1.06 (0.89, 1.268)*	*80/138*	*86/150*

Studies	Estimate (95% C.I.)	CONV-S	CONV-C
WJLCG	1.19 (0.90,1.56)	67/148	55/145
RTOG 9410	0.91 (0.64,1.29)	61/204	58/203
GMMA	1.00 (0.52,1.89)	5/14	4/14
GLOT	0.94(0.64,1.38)	40/103	24/101
Overall (I2=38%,P=0.39)	*1.14 (1.04, 1.30)*	*194/469*	*187/463*



Comment-2

I would be careful in the conclusion with stating that HYPO-RT-C could be used in clinical practice, as the safety still needs to be determined with the now standard use of immunotherapy. Additionally, I would disagree with the statement that HYPO-RT-C could be used as a control arm. Conclusions more in line with the available data should be presented. These certainly would be goals for future studies, but I would be careful to not deviate into recommending or advocating for such uses at this time.

Reply: We agree with your point. Therefore, we rewrote this part of the conclusion (please) see below:

"The indirect comparison of HYPO-RT outcomes with the standard treatment (CONV-RT) for locally advanced NSCLC suggests that HYPO-RT-C is feasible, convenient for patients, and further randomized clinical trials should consider it an experimental arm in the incorporation of new strategies, such as immunotherapy. These data can also be useful to design future clinical trials employing HYPO-RT."